DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, Maryland 20850

NOV - 7 2003

Via Federal Express
WARNING LETTER

Wesley Kinzie, M.D.
1401 Spanos Court, Suite #101
Modesto, California 95355

Dear Dr. Kinzie:

The purposes of this Warning Letter are to inform you of the objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site, to discuss your written response, dated June 24, 2003, to the deviations noted, and to request a prompt reply with regard to your corrective actions. The inspection took place during the period of April 28 through May 8, 2003, and was conducted by Mr. Carl Lee, an investigator from FDA's San Francisco District Office. The purpose of the inspection was to determine if your activities as a clinical investigator (CI) for [redacted] investigational study of the [redacted] System complied with applicable FDA regulations. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE) applications, Premarket Approval (PMA) applications, and Premarket Notification (510(k)) submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report submitted by the district office revealed serious violations of requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812 – Investigational Device Exemptions and Part 50 – Protection of Human Subjects, and Section 520(g) of the Act. You received a Form FDA 483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and these observations were discussed with you. The deviations noted on the Form FDA 483 and our subsequent review of the inspection report, as well as your response to the Form FDA 483 items are discussed below. The deviations noted include:

1. **Failure to follow the Investigator's Agreement, Investigational Plan and applicable FDA regulations; failure to ensure that informed consent is obtained in accordance with part 50 (21 CFR 812.100 and 812.110)**

In order to protect the rights, safety, and welfare of subjects under an investigator's care, CIs are required to ensure that investigations are conducted according to the following: the signed agreement, the Investigational Plan, and applicable FDA regulations. 21 CFR 812.100, 812.110(b). The CI must also comply with any conditions of approval imposed by the IRB or FDA. 21 CFR 812.110(b). The CI must also ensure that informed consent is obtained in accordance with part 50 and 21 CFR 812.100.

You failed to ensure that applicable FDA regulations were followed. Specifically, 21 CFR 56.108(a)(4) and 56.109(b) require that IRBs review and approve changes to the Investigational Plan. On May 7, 2001, the IRB initially approved the [redacted] System Investigational Plan and protocol. The inspection revealed that the study was conducted under a revised Investigational Plan dated October 2002 and a revised protocol dated May 2002. The revised Investigational Plan and protocol was not submitted to the institutional review board (IRB).

You also failed to ensure that informed consent was obtained in accordance with part 50, and to follow the Investigational Plan, which includes the informed consent form. (See 21 CFR 812.25(b)). On June 26, 2001, the IRB disapproved the revised June 15, 2001 Informed Consent Form. On July 31, 2001, the IRB approved the revised July 25, 2001 Informed Consent Form. The revised June 15, 2001 and July 5, 2001 Informed Consent Forms were utilized at your clinical site to obtain informed consent from study subjects. Eighteen study subjects signed the June 15, 2001 or July 5, 2001 Informed Consent Form which had not been approved by the IRB, as required by 21 CFR 50.27(a).

Another part of the Investigational Plan is the study protocol. (See 21 CFR 812.25(b)). You did not follow the protocol and as a result, three study subjects ([redacted] and [redacted]) who did not meet the inclusion/exclusion criteria were included in the study. Also, implantation with the investigational device, required by the study protocol, was not always performed at the times specified by the protocol. Subjects [redacted] and [redacted] did not receive the investigational device at the required [redacted] weeks or [redacted] calendar days time period from the pre-operative evaluation to operation. In addition, immediate post-operative evaluations for subjects [redacted] and [redacted] exceeded protocol timeframes.

You failed to comply with the signed Investigator's Agreement, as required by 21 CFR 812.110(b). The Investigator's Agreement requires you to report any deviations to the reviewing IRB, the sponsor and FDA. In addition, all non-emergency deviations from the FDA approved Investigational Plan require [redacted] from FDA, the sponsor and the appropriate IRB. You did not report the exceeded timeframes to any of these entities or have FDA approval.

2. **Failure to include all elements of informed consent (21 CFR 50.25)**

A review of one hundred percent of the Informed Consent Forms at your study site revealed that you failed to include all of the elements of informed consent as required by Federal regulations concerning the Protection of Human Subjects. The Informed Consent Forms (revised June 15, 2001; July 5, 2001; and May 15, 2002) did not include all of the study procedures. The May 15, 2002 revised Informed Consent Form did not disclose contact information for research related injury or questions. The basic elements required of informed consent are set forth in 21 CFR 50.25(a) and include requirements for a description of the procedures to be followed, and contact information for research-related injury and questions.

3. **Failure to maintain accurate, complete, and current records (21 CFR 812.140(a)); failure to comply with the signed Investigator's Agreement (21 CFR 812.110(b))**

You failed to maintain complete and accurate study records as required by 812.140(a). The following documentation was missing from the study records:

- all records of receipt and disposition of investigational device, as required by 21 CFR 812.140(a)(2)
- records of each subject's case history and exposure to the device, as required by 21 CFR 812.140(a)(3), including
  - pre/post-operative x-ray reports
  - x-ray reports for 6 and 12 month study visits
  - subject [redacted] revised, signed and dated Informed Consent Form (July 5, 2001), and
  - Several Case Report Forms (CRFs). For example, CRF 3 was missing from five out of fifteen subject records; CRF 8 for immediate post-operative evaluation was missing from four out of fifteen subject records; subject [redacted] record contained no CRF 8 for the pre-operative evaluation; [redacted] record contained no CRF 8 for 6 month study visit evaluation.

In your recordkeeping, you also failed to comply with the signed Investigator's Agreement, as required by 21 CFR 812.110(b). The Investigator's Agreement requires you to maintain a study monitoring visit log record, and to maintain all study records for a minimum of [redacted] years after completion of the study, suspension date or longer. Your files did not contain documentation of the on-site pre-study visit by the monitor.

We do not intend the list of deviations noted above to be an all-inclusive list of deficiencies that may have existed in your clinical study. It is your responsibility as a CI to ensure that your investigation is conducted in accordance with the signed investigational agreement, the Investigational Plan, and applicable FDA regulations.

Your written response, dated June 24, 2003, acknowledges the deviations noted on the FDA 483 and states, in most cases, that corrections will be implemented in the future. However, it does not adequately address each of the Form FDA 483 items. You do not specify what steps you are taking and how you will prevent future deviations. It is important for CIs to understand that unless the physical safety of a subject demands otherwise, treatment of study subjects must adhere to the requirements of the Investigational Plan.

During the close-out discussion, you acknowledged to Mr. Lee that you do not have an adequate understanding of your responsibility to maintain device accountability records. To assist you, please refer to the complete guidance in the "FDA Information Sheets, Guidance for Institutional Review Boards and Clinical Investigators," on the Internet at www.fda.gov/oc/ohrt/irbs/faqs.html#ClinicalInvestigations. Enclosed to assist you in better understanding of your responsibilities as a CI are copies of 21 CFR Parts 50, 56, and 812. These documents also are available electronically at www.access.gpo.gov/nara/cfr. Part 812 describes your responsibilities as a CI of an investigational device and Part 50 includes what is required to protect the welfare of study subjects. Part 56, Institutional Review Board, covers the responsibilities of IRBs and what an IRB expects from you as a CI, as well as their responsibilities to you.

Within fifteen (15) working days of receipt of this letter, you must provide this office with written documentation of the specific steps you have taken to correct these violations and bring your study activities into compliance with FDA regulations and to prevent recurrence of similar violations. Please send this information to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2094 Gaither Road, Rockville, Maryland 20850, Attention: Linda Godfrey.

In addition, please provide a list of your current investigational studies and include the name of the study sponsor and the date of IRB approval. Failure to respond to this letter and to take appropriate corrective action could result in enforcement action without further notice. In addition, FDA could initiate disqualification proceedings in accordance with 21 CFR 812.119.

A copy of this letter has been sent to FDA's San Francisco District Office, 1431 Harbor Bay Parkway, Alameda, California 94502. We request that a copy of your response be sent to that office.

If you have any questions you may contact Linda Godfrey at (301) 594-4723, ext. 134.

Sincerely yours,

for Timothy Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

Enclosures

cc: (purged copies)

[redacted]
Institutional Review Board
[redacted]

[redacted]
President/CEO
[redacted]